REMARKS

Applicants respectfully urge the Office's reconsideration of the outstanding rejections. For at least the reasons stated below, the outstanding Official Action fails to present a *prima facie* case of obviousness. Thus, Applicants traverse the rejections, and urge reconsideration and withdrawal of all outstanding rejections.

In addressing Applicants' previously presented arguments, the Official Action asserts that the Stamm reference teaches or suggests the claimed invention. Applicants respectfully disagree. The Office Action misconstrues the Stamm reference. The Office Action states that the Stamm reference teaches "the inert layer is covered with at least one layer containing a fenofibrate active ingredient in a micronized form and of at least 20% by weight of the hydrophilic polymer (a).

To clarify, Applicants note that the relevant portion of the cited passage states "said hydrophilic polymer making up at least 20% by weight of (a) ..." The reference to (a) is the combination of inert hydrosoluble carrier on which is a layer of micronized fenofibrate, a hydrophilic polymer, and optionally, a surfactant. The cited passage goes on to state that there may be additional layers (b) of one or several or outer phases or layers. Thus, the measurement of the hydrophilic polymer is such that it is at least 20% by weight of the inert hydrosoluble carrier, fenofibrate, hydrophilic polymer, and optional surfactant.

In an effort to compare apples to apples, Applicants have likewise confined the calculation of the percent of binding cellulose derivative to a percentage by weight of the neutral core, fenofibrate, surfactant, and binding cellulose derivative. In response to the preceding Official Action, Applicants amended the claim to state "wherein said binding cellulose derivative represents between 2 and 15% by weight of the ~~composition~~ combined neutral core, and the fenofibrate, surfactant, and binding cellulose derivative of the active layer." As such, Stamm's measurement "by weight of (a)" is substantially identical to Applicants' measurement "by weight of combined neutral core, fenofibrate, surfactant, and binding cellulose derivative." The addition of one or more layers of other ingredients on top of the active layer would have the same effect on Stamm as it would in Applicants' formulation, i.e., both would reflect an equal diminution of the percentage by weight of the cellulose polymer. While it is true that the 20% of Stamm is only with regard to component (a), and that several layers present would decrease the amount of cellulose in the layer, the same would hold true with the composition recited in Applicants' claimed method.

The Office Action also recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. Office Action, page 3. However, here, there is a failure to make a *prima facie* case as the rejection fails to either identify the specific elements of the claimed invention from the disparate references, and likewise fails to show any such teaching, suggestion, or motivation to combine the specific elements of the claimed invention in a manner as claimed. Specifically, there is no teaching or suggestion identified within the prior art for a method of reducing food effect in a patient by administering to a patient a pharmaceutical composition comprising micronized fenofibrate, surfactant, a binding cellulose derivative, wherein the composition is in the form of granules comprising a neutral core and an active layer surrounding the neutral core and wherein the binding cellulose derivative represents surrounding the neutral core and wherein the binding cellulose derivative represents between 2 and 15% by weight of the combined neutral core, fenofibrate, surfactant, and binding cellulose derivative of the active layer. None of the references teach or suggest such a low level of binding cellulose derivative. In fact, Stamm teaches the opposite. Stamm teaches that the binding cellulose derivative (hydrophilic polymer) must make up at least 20% by weight of the inert carrier and active layer (referred to by Stamm as (a). Stamm likewise characterizes that formulation as one wherein the hydrophilic polymer represents from 20 to 60% by weight, preferably 25 to 45% by weight (Stamm, column 5, lines 4-6). Stamm later emphasizes "the hydrophilic polymer represents preferably more than 25% by weight, based on the weight of (a)." Stamm, column 5, lines 11-12. Thus, Stamm teaches that the hydrophilic polymer must be at least 20% or more, and that preferred formulations have 25% or more. Stamm's teaching thus goes squarely against Applicants' claimed invention in that the amount of hydrophilic polymer must not be less than 20%, and that the formulation is improved by going substantially above that amount. In contrast, Applicants have shown improved bioavailability by using substantially lower quantities of binding cellulose derivative.

Applicants' use of lower quantities of binding cellulose derivative not only goes squarely against the teachings of Stamm, but in fact produces surprising and unexpected advantages and improvements in bioavailability of fenofibrate. It is a longstanding and well recognized problem in the art to improve the otherwise low bioavailability of fenofibrate. Indeed, the cited references themselves acknowledge the poor bioavailability, and address various approaches toward enhancing bioavailability. For example, Curtet states at column 1, lines 24-27, that "it is therefore desirable to develop a dosage form in which the bioavailability of the fenofibrate is improved and which can be administered only once a day." Curtet attempts to solve this problem by co-micronizing fenofibrate with a surfactant. Curtet, column 1, lines 47-49.

Stamm, likewise, recognizes the need for improved bioavailability of fenofibrate formulations. Stamm, column 1, lines 26-29 ("Indeed, due to its poor hydrosolubility, fenofibrate is poorly absorbed in the digestive tract and consequently its bioavailability is incomplete, irregular and often varies from one person to another."). Stamm, however, takes a different approach than Curtet.

Stamm acknowledges and disparages the approach of co-micronizing fenofibrate with a surfactant. Stamm notes that such approaches "are not completely satisfactory inasmuch as it does not lead to complete bioavailability of the active ingredient, and suffers from several disadvantages." Stamm, column 1, lines 64-67. Indeed, Stamm states that the problem is better resolved by resort to a method for preparing a composition by spraying a suspension of the active ingredient onto an inert hydrosoluble carrier. Stamm, column 2, lines 14-18. Stamm, however, teaches that this enhancement can only be achieved by using a hydrophilic polymer at at least 20% by weight of the combined inert carrier fenofibrate, hydrophilic polymer, and optional surfactant.

In contrast, Applicants have gone against that teaching and substantially reduced the amount of binding cellulose derivative to an amount equal to 2 to 15% by weight of the inert carrier, fenofibrate, surfactant, and binding cellulose derivative. Applicants have achieved surprising and unexpected results in doing so. Applicants submit herewith a copy of the Declaration of George Bobotas, as it was submitted in related U.S. application Serial No. 10/030,262. The Bobotas Declaration shows that the formulations recited in the present claims improve the dissolution profile and bioavailability of fenofibrate in a surprising and unexpected fashion compared to the prior art. Specifically, and contrary to the teachings of Stamm, fenofibrate dissolution and bioavailability is enhanced by decreasing, rather than increasing, the relative concentration of cellulose derivative. This is illustrated in the data presented in the Bobotas Declaration. For example, the Declaration shows that formulations as described in the claimed invention having 130 mg fenofibrate achieve C_{max} about the same as prior art 200 mg fenofibrate formulations (i.e., Tricor). See, Bobotas Declaration, Table I.

The instant formulations have Mean $AUC_{0-\infty}$ per milligram fenofibrate of 1,018 (130 mg) as compared to prior art formulations of 811 (200 mg Tricor). Likewise, Mean $AUC_{0-\infty}$ per milligram fenofibrate of the instant formulations (120 mg and 144 mg fenofibrate) were compared with the prior art Tricor 160 mg fenofibrate, and were shown to have surprisingly improved bioavailability, i.e, 962 (120 mg) and 920 (144 mg) as compared to 802 (160 mg Tricor). Bobotas Declaration, Tables II and VI. Thus, the formulations of the present invention provide surprising and unexpected improvements in fenofibrate bioavailability. The fact that the formulations described in the instant claims go squarely against the teachings of Stamm, and nonetheless produce surprising and unexpected improvements in bioavailability is the very epitome of nonobviousness. Thus, reconsideration and withdrawal of the rejection is respectfully requested.

Additionally, and as argued previously, the remaining references fail to teach or suggest the claimed invention. As discussed above, Curtet teaches pharmaceutical compositions containing fenofibrate co-micronized with a solid surfactant. Stamm disparages such co-micronized formulations, and explains how they do not sufficiently improve bioavailability. Thus, one would not have been motivated to look to the teachings of Curtet alone or in combination with Stamm. Further, Curtet does not teach the use of a neutral microgranule, but rather teaches a wet granulated mixture. See, e.g, Curtet, column 2, lines 5-20. Nothing within the teaching of Curtet alone or in combination with Stamm has been shown to teach or suggest the present invention. Specifically, there has been shown no teaching, suggestion or motivation to modify either of Stamm or Curtet to arrive at the claimed formulation as recited in the instant claims.

The Office Action raises Boyer as teaching administering micronized fenofibrate to a set population with high triglyceride wherein the fenofibrate formulation has an inert core comprising cellulose binder. The rejection asserts that Boyer teaches the percent of cellulose binder as 12.5%. Applicants respectfully disagree. Boyer describes at column 2, lines 52-55 that inert cores are "dampened with an alcohol solution containing 12.5% by weight of a methacrylic polymer." (emphasis added). The 12.5 % polymer is measured relative to the alcohol solution not the resulting formulation of the inert core, fenofibrate, surfactant, and polymer. The 12.5% by weight of polymer in the alcohol solution tells the reader nothing about the quantity of polymer in the resulting formulation. It certainly does not teach or suggest the claimed range for binding cellulose derivative. As there is no reference to the percent polymer relative to the combined composition of inert core, fenofibrate, binding cellulose derivative, and surfactant, there is no teaching or suggestion of the formulation recited in the instant claims.

Similarly, the rejection misconstrues the Stamm reference at column 6, lines 36-37. As explained previously, this too is a reference to a liquid mixture (suspension) that is used to fabricate the pharmaceutical formulation. Thus, the reference to 5 to 40% by weight of a hydrophilic polymer does not refer to the weight of the formulation, much less that of the specific neutral core, fenofibrate, binding cellulose derivative, and/or surfactant. This instead is a separate suspension, and the concentration in that suspension says nothing about the concentration of that constituent in the final pharmaceutical formulation.

The rejection also asserts that, although the reference teaches different ratios of fenofibrate to binding cellulose derivative, the determination of ranges having optimum therapeutic index is within the level of one of ordinary skill in the art. Applicants respectfully disagree. Here, the Stamm reference squarely teaches away from the present invention. The Stamm reference teaches that the formulation must comprise at least 20%, and preferably 25% or more, of a hydrophilic polymer relative to the combination of the inert core, fenofibrate, hydrophilic polymer, and/or surfactant. The reference must be considered as a whole. Thus, this is not an instance of finding optimal therapeutic index. If so, Applicants would have searched, consistent with the teaching of the reference, for optimal ranges greater than 25% of binding cellulose derivative. Instead, Applicants went against the teaching and suggestion of the cited reference.

Additionally, the rejection overlooks the surprising and unexpected results as illustrated in the enclosed Bobotas Declaration. Among other things, the Bobotas Declaration shows that with the claimed formulations, one can actually reduce the concentration of fenofibrate and still produce a substantially bioequivalent effect relative to prior art formulations having greater concentrations of active agent.

The rejection has also cited the HHS/CDER reference as teaching the effect of food on the absorption of certain active agents. Likewise, the rejection relies upon www.pslgroup.com/dg. Applicants do not contest that the food effect is acknowledged within the art, and that certain active agents are known to suffer more than others from this food effect. Indeed, this is specifically what the present invention is directed to address. That is, Applicants have set about to develop a pharmaceutical formulation for an active agent known to be profoundly susceptible to the food effect, and have nonetheless produced a pharmaceutical formulation that diminishes, if not eliminates, this food effect. The acknowledgement that there is such a food effect is no more than an acknowledgement of an existing problem prevailing in the art for which there is no proffered solution. The HHS/CDER document does no more than document its existence, and explain that certain methodologies can be used to detect and/or measure the food effect. It does not present methodologies for eliminating it. Such methodologies would be essential to any showing of obviousness in view of the cited art.

Finally, the Munoz reference likewise fails to satisfy the deficiencies of the various cited references. Munoz merely asserts that the digestive absorption of Lipanthyl is improved relative to the prior art and may have reduced food effect. However, as demonstrated in the Bobotas Declaration, the 200 mg micronized Lipanthyl (aka TRICOR) does not achieve the bioavailability of the instant invention. In fact, the Munoz reference, in studying 200 mg Lipanthyl, is merely an assessment of the formulation that is disclosed in the Stamm reference.

As to the double patenting rejection, Applicants submit that the rejection is improper. Claims 1-34 of U.S. Patent No. 7,101,574 are directed to a pharmaceutical composition in the form of granules. The instant claims are directed to a method of treatment. While it is true the methods of treatment of the instant claims incorporate a formulation similar to that of the '574 patent, Applicants assert that there is no double patenting. However, to expedite examination and disposition, Applicants submit herewith a Terminal Disclaimer of the instant application over that of U.S. Patent No. 7,101,574. Likewise, without conceding the rejection for obviousness type double patenting with respect to co-pending related application Serial No. 11/509,806, Applicants likewise submit a Terminal Disclaimer with respect to that application to expedite examination and disposition.

In view of the foregoing amendments and remarks, applicants respectfully request reconsideration and withdrawal of all outstanding rejections. Applicants submit that the claims are now in condition for allowance, and respectfully request formal notification to that effect. If, however, the Examiner perceives any impediments to such a notice of allowability, whether substantive or formal, the Examiner is encouraged to call Applicants' attorney at the number provided below. Such informal communication will expedite examination and disposition of this case.

Respectfully submitted,

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